EXPERIMENTAL COMPARISON OF RADIOACTIVE AGENTS FOR STUDIES OF THE PLACENTA

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The localization of 15 different radiopharmaceuticals in the placenta, fetus, and various organs was studied by tissue radioassay in the pregnant rabbit. The highest placental concentration was obtained in the rodent with carrier-free ^{113m}In as labeled transferrin; however, even small amounts of carrier indium (10 μg/kg) lowered its placental uptake. Other transferrin-bound radiopharmaceuticals did not localize to the same degree in the placenta. In a comparison of five different radioactive colloids, only a radiocolloid of ^{159}Dy-gluconate exhibited a placental concentration comparable to labeled serum albumin, presumably due to the reticuloendothelial function of that organ.

Six different short-lived radiopharmaceuticals were compared by scintillation camera imaging following successive intravenous administrations in a pregnant rhesus monkey near term. Images of the placenta were better with ^{99m}Tc-albumin than with ^{113m}In-transferrin, but the best images were obtained with ^{99m}Tc-labeled autologous red blood cells. Of two skeletal imaging agents, ^{99m}Tc-EHDP apparently crosses the placental barrier to enter the fetal skeleton to some degree whereas larger molecular weight ^{99m}Tc-polyphosphate does not.

The in vivo localization of the placenta before delivery has been the subject of numerous articles over many years. The usual indication is to confirm or rule out placenta previa in third trimester bleeding. Knowledge of the placental site is desirable also before Caesarean section or amniocentesis. Soft-tissue radiography, contrast radiography, thermography, ultrasound, and radioisotopic methods have been offered as means of identifying the placenta. Since the original work of Brown and Veall (*1*) in 1950 using ^{24}Na, a variety of gamma-emitting radiopharmaceuticals with better physical characteristics have been explored. These for the most part have been agents that tend to remain within the maternal vascular space such as ^{131}I-albumin (*2,3*) or ^{51}Cr-labeled red blood cells (*4*). Within recent years, radionuclides with a short physical half-life, such as ^{99m}Tc-pertechnetate (*5*), ^{99m}Tc-albumin (*6–8*), ^{113m}In-transferrin (*9,10*), or ^{11}C-labeled red blood cells (*11*), have been favored because sufficient amounts of these materials may be administered to image the placental blood pool by rectilinear scanners or scintillation cameras.

In selecting an "optimal" agent for delineation of the placenta by external gamma detection, the following criteria should be considered: (A) the absorbed radiation dose to mother and fetus; (B) a high concentration in the placenta; (C) a low concentration in the fetus and uterine wall; and (D) no renal excretion, to avoid obscuration of a low-lying placenta.

In the present work, tissue distribution values for a variety of radiopharmaceuticals were determined in pregnant rabbits because of the paucity of published data on this subject. Radioactive colloids were included in this study in view of the work of Goldmann (*12*) and Wislocki (*13*) on the staining of rodent placentas by colloidal vital dyes. Although the placental localization of radioactive agents bound to plasma proteins has been the subject of previous investigations, the concentration of radioactive colloids in the placenta has not been measured previously. In addition, several radiopharmaceuticals were evaluated by both rectilinear scanning and cam-

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TABLE 1. DISTRIBUTION OF RADIOPHARMACEUTICALS IN PREGNANT RABBITS: MEAN VALUES AT 1 HR AS PERCENT DOSE/1% BODY WEIGHT

No. of animals	42	6	2	2	6	6	8	5	4	2
Agent	^{125}I-albumin	^{113m}In-carrier-free	^{114m}In with carrier	^{59}Fe-citrate	^{67}Ga-citrate	^{51}Cr-chloride	^{57}Co-vit. B_{12}	$Na^{131}I$	$^{99m}TcO_4^-$	^{99m}Tc-long-chain-colloidal poly-phosphate
Blood	10.5	6.79	8.67	3.11	7.81	2.16	12.8	1.11	1.37	1.13
Liver	3.23	2.24	2.7	1.00	1.52	3.95	2.11	0.35	0.99	19.1
Spleen	3.75	1.96			1.40	8.96	1.91	0.61	0.43	
Kidney	4.17	6.25	6.88	2.67	4.31	2.27	3.93	2.07	2.60	5.34
Bone marrow	5.84	4.27	4.02	13.4	1.88	2.62	4.30	0.61	0.54	7.74
L. gut & contents	0.39	0.29	0.89	0.92	0.33	0.52	0.33	0.53	0.44	0.29
S. gut & contents	0.92	0.93	0.97	1.07	0.53	0.61	0.82	0.73	0.90	0.25
Muscle	0.17	0.30	0.33	0.22	0.21	0.18	0.15	0.15	0.12	0.06
Placenta	3.75	25.6	13.6	4.74	12.0	1.87	4.44	3.52	5.95	0.06
Uterus	1.60	1.08			1.75	1.01	1.34	1.38	2.81	
Fetus	0.63	0.03	0.02	9.87	0.06	0.05	0.04	2.11	4.84	0.02
Placenta/fetus	5.95	853	59.0	0.50	200	37.4	111	1.67	1.23	3.0
Placenta/blood	0.36	3.77	1.60	1.50	1.54	0.87	0.35	3.17	4.34	0.05

era imaging of a pregnant rhesus monkey since this primate has a hemochorial placenta similar in structure to that of the human.

MATERIALS AND METHODS

Organ distribution studies of 15 different radiopharmaceuticals (listed in Tables 1 and 3) were carried out. Technetium-99m-sulfur colloid was prepared from a kit formulated in our laboratory by acid hydrolysis of sodium thiosulfate using gelatin as the stabilizer. This colloid contained less than 2% free pertechnetate as determined by paper chromatography. The ^{131}I-microaggregated albumin was prepared from commercial ^{131}I-MAA by ultrasonification. The particle size of this material after sonification was found to be less than 1 micron as determined by light microscopy. It also contained as much as 10% free iodide. This fact was taken into account in calculations on organ distribution of this material by applying corrections from the ^{131}I-sodium iodide distribution data. Dysprosium-159-gluconate with lutetium was prepared as follows: ^{159}Dy in dilute HCl was obtained from commercial sources*. Lutetium was obtained as chloride salt† and dissolved in dilute hydrochloride solution. The ^{159}Dy was then mixed with carrier lutetium, and ten times its weight of sodium gluconate was added, mixed well, and the pH was adjusted to 6–6.5 using dilute sodium hydroxide. Indium-113m-gluconate was prepared in exactly the same way except that ^{113m}In, as eluted from a tin-indium generator, was substituted for ^{159}Dy. Two different polyphosphates* were labeled with ^{99m}Tc and stannous ions according to the method already reported (*14*). The nuclides ^{113m}In and ^{114m}In were used in dilute HCl solution at pH 1.3–1.5. All other materials listed in Table 1 were obtained from commercial sources.

New Zealand albino rabbits in the third trimester of pregnancy (as determined by breeding date) were used for the organ distribution studies. The compound to be studied was administered intravenously together with 10–20 μCi of ^{125}I-human serum albumin. The latter was used as a biological standard for comparison between the different groups of animals. The following specific doses were given: 50 μCi ^{113m}In; 5 μCi ^{114m}In (with carrier indium 5 μg/kg); 1–2 μCi ^{57}Co-vitamin-B_{12}; 100 μCi $^{51}CrCl_3$; 10–15 μCi ^{99m}Tc compounds; and 10–15 μCi ^{159}Dy 5 μCi (with carrier lutetium 100 μg/kg). For ^{113m}In-gluconate, the same quantity of 100 μg/kg of stable lutetium was used. Most of the animals were killed 1 hr after injection of the radiopharmaceutical since this was considered the maximum time interval from injection to the completion of a scanning procedure. However, the four animals injected with

* International Chemical and Nuclear Corporation.
† Alfa Inorganics.

* Calgon Corporation, Pittsburgh, Pa. Two different polyphosphates were labeled: (A) Linear polyphosphates, estimated chain length 5,000; estimated molecular weight 500,000 (used as a colloid) and (B) linear polyphosphates, estimated chain length 50; estimated molecular weight 5,000 (used for bone imaging).

^{159}Dy-gluconate were killed at 3 hr to allow ample time for this radiocolloid to clear from the bloodstream. The numbers of animals used for each study are listed in Tables 1 and 3. Multiple tissue samples were obtained from all major organs including liver, spleen, kidney, large intestine, small intestine, skeletal muscle, uterine wall, bone marrow, and blood. Urine samples were taken in toto whenever available. Four whole placentas and four fetuses were obtained from each animal for radioassay.

The samples were weighed and then counted in a dual-channel Nuclear-Chicago automatic well counter along with appropriate standards. All the tissue specimens except the fetuses were counted in this way. The latter were counted for 10 min in a heavily shielded chamber with a 3 × 3-in. NaI(Tl) crystal and a Tullamore 400-channel multichannel analyzer along with radioactive standards of identical geometry. Compton corrections were made as necessary when more than one radioisotope was used in the same animal. To calculate the total activity in the whole organ, the total blood mass was assumed to be 7% of the body weight, the muscle mass 43%, and the active bone marrow 2.2%.

A rhesus monkey in the third trimester of pregnancy was judged to be approximately 140 days pregnant at the time of our study. (The normal gestation period for this species is 164 days.) The monkey was given single intravenous doses of 4–8 mCi of each of the following agents, administered on separate days: ^{99m}Tc-labeled autologous red blood cells; ^{99m}Tc-human serum-albumin (*6*); ^{99m}Tc-sulfur colloid; ^{99m}Tc-polyphosphate*; and ^{99m}Tc-ethane-1 hydroxy-1-, 1-diphosphonate (EHDP); and ^{113m}In in acid solution.

Ten milliliters of blood were obtained from the

* Calgon Corporation, Pittsburgh. Linear polyphosphate, estimated chain length 46; estimated molecular weight 4,600. This material has been used previously for skeletal imaging (*14*).

TABLE 2. DISTRIBUTION OF RADIOPHARMACEUTICALS IN PREGNANT RABBITS: MEAN VALUES AT 1 HR AS PERCENT DOSE IN WHOLE ORGAN

Agent	^{125}I-albumin	^{113m}In-carrier-free	^{114m}In with carrier	^{59}Fe-citrate	^{57}Co-vit. B_{12}	^{51}Cr-chloride	^{67}Ga-citrate	Na^{131}I	$^{99m}TcO_4^-$	^{99m}Tc-long-chain-colloidal poly-phosphate
Blood	73.8	47.6	60.7	21.8	89.6	15.1	54.7	7.77	9.59	7.97
Liver	8.31	5.99	7.69	3.02	5.59	15.5	4.03	0.95	2.84	56.1
Spleen	0.15	0.08			0.08	0.32	0.07	0.02	0.02	
Kidney	1.91	2.91	3.06	1.60	1.80	1.25	2.03	0.95	1.37	3.21
Marrow	12.8	9.38	8.85	29.6	9.47	5.77	5.38	1.34	1.19	17.0
Muscle	7.22	12.7	14.2	9.44	6.65	7.82	8.96	6.24	5.30	2.38
Urine	1.29	0.49			0.44	14.6	4.87	0.25	0.78	
Placenta (single)	0.27	1.97	0.79	0.28	0.26	0.15	0.68	0.28	0.35	0.04
Fetus (single)	0.43	0.03	0.01	2.43	0.01	0.03	0.02	2.42	1.59	0.004

TABLE 3. DISTRIBUTION OF COLLOIDAL RADIOPHARMACEUTICALS IN PREGNANT RABBITS: MEAN VALUES AT 1 HR AS PERCENT DOSE/1% BODY WEIGHT

No. of animals	5	6	6	4	5
Agent	^{198}Au-colloid	^{99m}Tc-sulfur colloid	^{131}I-microaggregated albumin	^{159}Dy-gluconate (3 hr)	^{113m}In-lutetium carrier
Blood	0.12	0.25	0.61	3.17	5.19
Liver	30.0	35.5	25.0	10.9	8.14
Spleen	10.5	61.2	32.7		5.27
Kidney	0.15	3.67	1.28	4.86	3.54
Marrow	13.6	13.0	6.82	13.2	9.76
L. gut & contents	0.01	0.04	0.18	0.39	0.10
S. gut & contents	0.01	0.16	0.34	0.33	0.38
Muscle	0.01	0.11	0.09	0.06	0.09
Placenta	0.13	1.59	1.34	4.93	17.7
Uterus	0.02	0.09	0.61		0.65
Fetus	0.00	0.11	0.61	0.01	0.02
Placenta/fetus		14.5	2.20	353	885
Placenta/blood	1.08	6.36	2.20	1.60	3.41

TABLE 4. DISTRIBUTION OF COLLOIDAL RADIOPHARMACEUTICALS IN PREGNANT RABBITS: MEAN VALUES AT 1 HR AS PERCENT DOSE IN WHOLE ORGAN

Agent	^{198}Au-colloid	^{99m}Tc-sulfur colloid	^{131}I-microaggregated albumin	^{159}Dy-gluconate (3 hr)	^{113m}In-lutetium carrier
Blood	0.86	1.77	4.31	22.2	36.4
Liver	86.9	93.2	52.7	29.5	21.8
Spleen	0.47	2.48	1.58		0.29
Kidney	0.08	1.58	0.52	2.31	1.72
Marrow	29.9	28.8	15.0	29.0	21.5
Muscle	0.42	1.01	4.24	2.35	3.73
Urine	0.01	0.47	8.34	0.60	0.22
Placenta (single)	0.01	0.10	0.11	0.43	1.25
Fetus (single)	0.00	0.01	0.58	0.01	0.01

monkey and labeled with ^{99m}Tc by the method of Nouel and Brunelle (*15*) using stannous citrate and EDTA. Then the red cells were washed and centrifuged three or four times until less than 1% of the radioactivity was removed in the last washing. For the other radiopharmaceutical preparations labeled with ^{99m}Tc, the fraction of free pertechnetate was determined by paper chromatography in 0.85% methanol in isotonic saline and was found to be always less than 5%. The ^{99m}Tc-EHDP was prepared as described elsewhere (*16*). The preparation of the other compounds administered was described earlier. With each agent, rectilinear scans were obtained in the anterior, posterior, and both lateral projections using an Ohio-Nuclear dual-probe 5-in. scanner. The C collimator was used for the ^{99m}Tc-albumin and ^{113m}In scans, and the 35L collimator for the others. In addition, images were obtained in multiple projections with the Nuclear-Chicago HP gamma camera using the 410-keV medium-fine parallel-hole collimator for ^{113m}In and the high-resolution collimator for all of the ^{99m}Tc agents. Three hundred thousand counts were obtained in each image.

RESULTS

The results of the rabbit studies are presented in Tables 1–4. Radiographs and camera images of the rhesus placenta in the anterior, posterior, and lateral views are shown in Figs. 1–4.

The larger particle radiocolloids, ^{99m}Tc-sulfur colloid and ^{131}I-macroaggregated albumin, concentrated poorly in the placenta. Gold-198 colloid, one of the smallest radioactive colloids available, also showed very poor placental localization. The rare earth colloid ^{159}Dy-gluconate reached a higher level in the placenta, slightly above the value for iodine-labeled serum albumin.

Among the other materials, carrier-free ^{113m}In, which labels transferrin in vivo when injected at a pH below 2.5, shows the highest placental concentration. It is interesting that small amounts of carrier in the ^{114m}In preparation decreased the placental activity by a factor of two compared with carrier-free ^{113m}In. The placental content of ^{113m}In with lutetium carrier was also less than that of carrier-free ^{113m}In. Iron-59-citrate, ^{57}Co-vitamin-B_{12}, and ^{67}Ga-citrate localized well in the placenta. All three are bound to plasma protein components. On the contrary, ^{51}Cr-chloride localized poorly in the placenta, although it also is protein-bound. The localization of Na^{131}I and ^{99m}Tc-pertechnetate in the placenta is nearly as high as that of the "blood pool" agent, ^{125}I-albumin, but their fetal concentrations are much greater.

On comparing the images obtained on the preg-

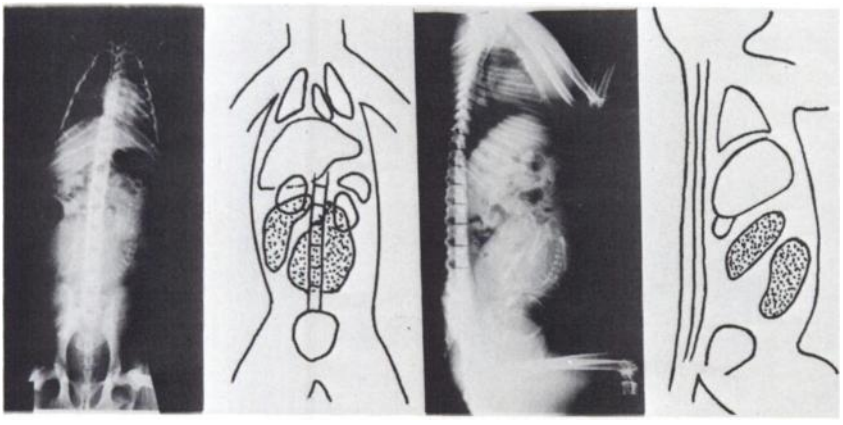

FIG. 1. AP and lateral radiographs of pregnant rhesus monkey. Line drawings of major organs obtained from tracings of radioisotopic images with various agents. Bidiscoid placenta shown as stippled areas.

nant rhesus monkey, the best resolution of the placenta was seen with ^{99m}Tc-labeled red blood cells. Technetium-99m-human serum albumin and ^{113m}In-transferrin also showed the placental site well. Whereas adequate visualization was obtained with ^{113m}In on the gamma camera using the 410-keV medium-fine hole collimator, edge penetration and collimator artifact did compromise image quality as compared with ^{99m}Tc red cells and albumin. The three remaining ^{99m}Tc agents—sulfur colloid, polyphosphate (MW 5000), and EHDP—did not show adequate placental accumulation for good image quality. An interesting difference was noted between the two skeletal imaging agents—^{99m}Tc-polyphosphate did not cross the placenta in amounts sufficient to visualize the fetal skeleton whereas ^{99m}Tc-EHDP did.

DISCUSSION

The tissue distribution results in rabbits are compatible with the current concept that the placenta is a lipoid barrier functionally resembling the blood-brain barrier, which is completely permeable only to lipid-soluble drugs (*17*). Most drugs with a molecular weight less than 600 cross the placenta easily, whereas it is relatively impermeable to water-soluble drugs with a molecular weight exceeding 1,000. Free radioactive alkaline cations of $^{24}Na^+$, $^{86}Rb^+$, and $^{45}Ca^{2+}$, and anions such as $^{18}F^-$, $^{14}CO_2^{2-}$, $^{131}I^-$, $^{35}SCN^-$, or $^{75}SeO_3^{2-}$ localize in the same tissues in the fetus as in the mother in somewhat lower concentrations and therefore cross the placental barrier (*18*). The placental concentration of Na^{131}I in the present study is surprisingly high, approaching that of ^{125}I-albumin. However, the high fetal concentration observed is undesirable. Likewise, both the placental and fetal concentrations of ^{99m}Tc as a pertechnetate ion are relatively high. Although this latter material has been used previously for placental localization in humans for convenience, agents labeled with this nuclide, which do not cross the placenta so readily, are preferable because "on-site" irradiation of fetal tissues such as the thyroid is avoided.

Of the two complexes of ^{99m}Tc recently developed for skeletal imaging, the larger molecular weight agent, ^{99m}TcSn complex of linear chain polyphosphate (MW 4,600–5,000) apparently did not cross the placental barrier, whereas the smaller molecules of the ^{99m}TcSn complex of EHDP (MW 190 unlabeled) showed some localization in the fetal skeleton. Neither agent exhibited a high uptake in the placenta.

Various radioactive ions that are transported in the maternal blood largely bound to transferrin (*19*) (a beta-pseudoglobulin, MW 90,000) exhibited

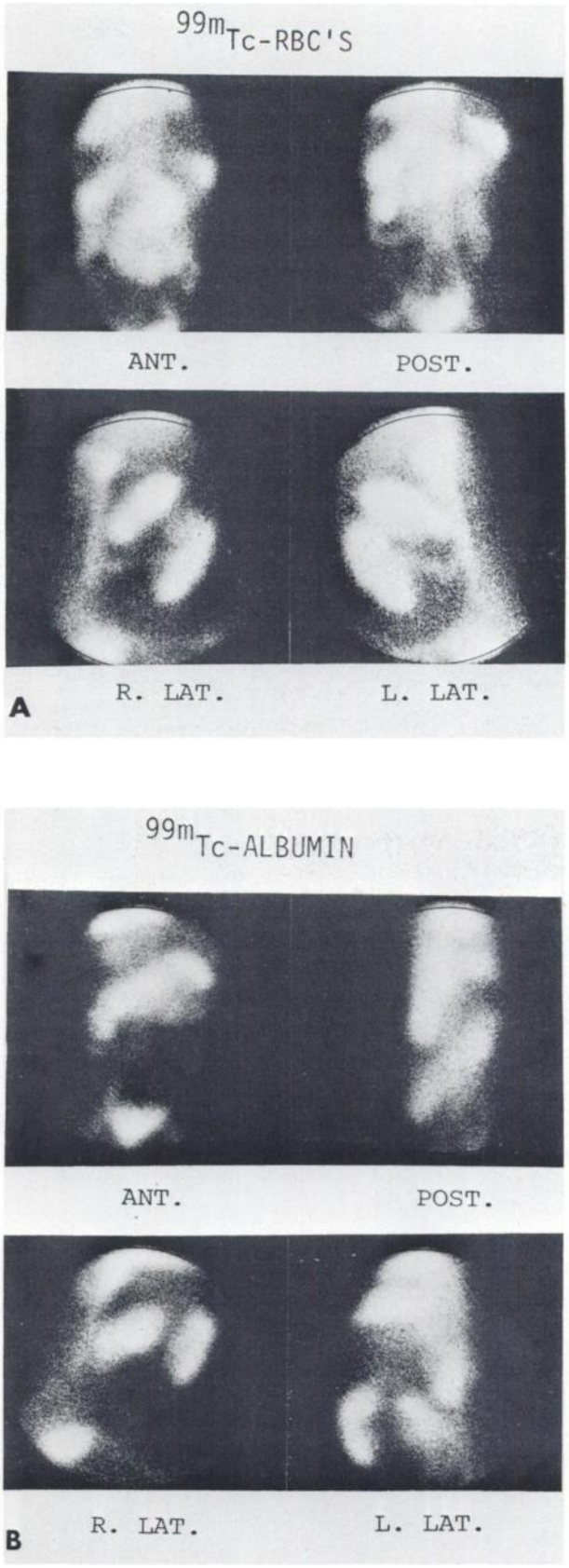

FIG. 2. Camera images of pregnant rhesus monkey. Anterior portion of placenta in anterior projections is shown better with ^{99m}Tc-labeled red cells (A) than with labeled albumin (B).

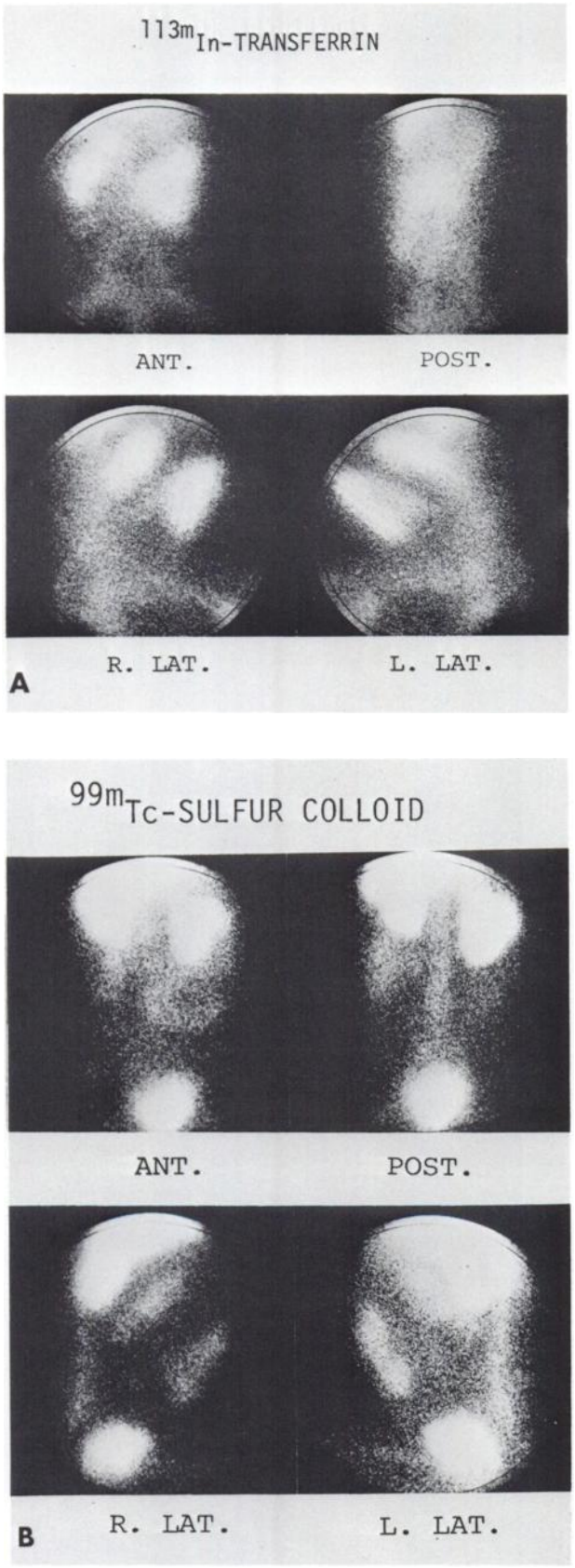

FIG. 3. Camera images of pregnant rhesus monkey. Note absence of bladder activity with ^{113m}In-transferrin (A) and poor placental visualization with ^{99m}Tc-colloid (B).

marked individual differences. In the rabbit study, about 10% of an administered dose of ^{59}Fe per 1% body weight was found in the fetuses and 5% per 1% body weight in the placenta at 1 hr. In a similar previous study in the rat, 50% was found in the fetuses and 5–10% in the placentas at 1 hr (*20*). There was a progressive increase in fetal concentration from 1–5 hr in the rat and a higher placental transfer of iron in late pregnancy than in early pregnancy. In another comparative study of near-term pregnant females with a hemochorial placenta (such as the rhesus monkey, rabbit, and rat) the fetuses contained 5% or more of the injected ^{59}Fe, whereas species with other types of placentation such as the dog or cat showed a much lower fetal transfer of iron of 0.1% or less (*21*). The transfer of iron into the fetus was considerably lower in primates than in rodents. All of the above studies indicate that in the hemochorial placenta ^{59}Fe is rapidly released from plasma transferrin and is rapidly transported into the fetal circulation.

Carrier-free ^{113m}In within an acid pH range of 1.5–2.5 binds specifically to transferrin in vivo after intravenous injection (*22*). The present study indicates that the placental concentration in the rabbit at 1 hr is higher than for any other agent tested (26%/1% body weight) and the fetal concentration very low (0.03%/1% body weight). In the nonpregnant state the transferrin binding of carrier-free ^{113m}In is so complete that it may be used for plasma volume determinations provided that the transferrin is not already saturated with iron (*22*). In the pregnant state the radioactive indium reaching the placenta is released from transferrin, does not cross into the fetal circulation, but accumulates in the placenta. The presence of very small amounts of carrier indium (10 μg/kg) significantly lowers the placental concentration of indium without much change in the blood levels or fetal concentration. Similarly, the presence of a small amount of another trivalent cation, the rare earth lutetium (100 μg/kg), also lowered the placental uptake of the radioactive indium, probably by converting it to a colloid.

Neither indium nor iron bound to transferrin actually follow the metabolic pathway of this protein. Transferrin labeled with ^{125}I has an initial plasma clearance half-time of about 1 day compared with 6 hr for indium and 1–2 hr for iron (*22*). This protein becomes about equally distributed in the extravascular and intravascular spaces, and about 40% remains in the plasma with a half-time of 6–8 days. In contrast, less than 4% of ^{113m}In bound to transferrin remains in the plasma at 2 days (*22*). In the rat, the placentas concentrate only about 9%

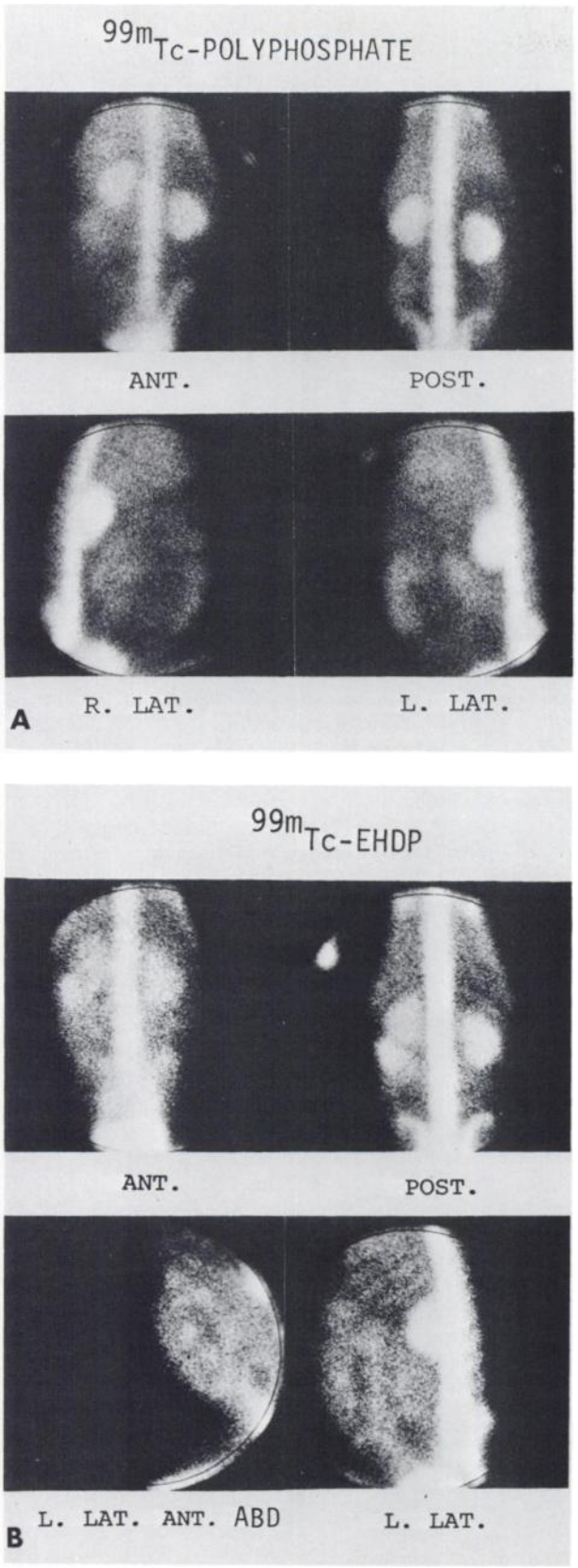

FIG. 4. Camera images of pregnant rhesus monkey. Considerable activity is seen in fetus on both lateral projections with ^{99m}Tc-EHDP (B) but not with ^{99m}Tc-polyphosphate (A). Poor placental visualization on both studies.

of an intravenous dose of ^{125}I-transferrin, and the fetuses contain about 1% (*20*).

Radioactive carrier-free gallium injected as citrate is largely bound to plasma proteins in the bloodstream. In vitro equilibrium dialysis experiments with ^{72}Ga-citrate indicate that about 97% of the radioactivity is protein-bound (*23*). According to one study of patients' blood samples 3–72 hr after injection, about 70% is loosely associated with albumin and some globulins; the undialyzable remainder is bound primarily to transferrin but also to haptoglobin as indicated by cross immunoelectrophoresis (*24*). The placental concentration of ^{67}Ga-citrate in the rabbit is much higher than for ^{125}I-albumin but not as high as with radioactive indium. Another nuclide, ^{51}Cr, injected as either labeled serum albumin or as chromic chloride, becomes bound to transferrin, and its slow component of plasma disappearance has a half-time of 8 days, similar to iodine-labeled transferrin (*25*). Its blood and placental concentrations in the rabbit are, however, much lower than the other transferrin-bound ions.

Trace quantities of ^{57}Co-vitamin B_{12} after intravenous injection behave as a blood pool agent in the rabbit. Although its blood disappearance is more rapid in humans, it does become bound initially to transcobalamin II (a beta globulin, MW 38,000) with a plasma clearance half-time of 1½ hr. Later it binds predominantly to transcobalamin I (an alpha globulin, MW 121,000) with a slower plasma clearance half-time of about 9 days (*26*). In the rabbit the blood and placental levels are slightly higher than those of ^{125}I-albumin, but the placental-to-blood ratios are identical. At 1 hr, the fetal concentration is much lower than for ^{125}I-albumin.

Qualitative studies of the past provided evidence for reticuloendothelial function of the placenta. After Goldmann's initial work in 1909 (*12*), Wislocki in 1921 (*13*) observed that finely dispersed colloidal dyes like trypan blue stained most maternal organs, densely stained the placentas, but did not stain the fetuses or amniotic fluid unless massive doses were injected intravenously. The degree of staining of the fetuses in cats was even less than in rodents. Later, Fischer (*27*) injected stannic oxide colloid (mean particle size less than 1 micron) in intravenous doses of 388 mg/kg in rabbits as a radiographic contrast medium visualizing the liver and spleen. In one pregnant rabbit near term, the colloidal particles visualized the placenta. Macrophages of the placenta, first found by Hofbauer in 1903, were described in detail by Fox (*28*). They are round or oval cells, 10–40 microns in diam, found in about 2% of villi, in the placental septa, and are abundant in the basal

plate and chorionic plate. They are especially numerous in patients with rhesus incompatibility and diabetes mellitus, and phagocytose both dyes and meconium.

Wislocki observed previously that the smaller trypan blue particles were phagocytosed by the placenta in guinea pigs more readily than larger carbon particles. The present quantitative studies of the distribution of several radioactive colloids indicate that the immeasurably small particles of the radiocolloid of ^{159}Dy have a greater tendency to accumulate in the placenta than larger colloidal particles such as ^{99m}Tc-sulfur colloid (particle size less than 1 micron) or colloidal ^{198}Au (particle size 5–50 millimicron). The ^{159}Dy radiocolloid was the only colloidal material found in this study with a placental concentration slightly better than ^{125}I-albumin: all other colloids showed a relatively poor placental uptake. The fetal concentrations of the radioactive colloids were low except for ^{131}I-labeled microaggregated albumin. This material was metabolized so rapidly, however, that the higher fetal radioactivity was probably due to free radioiodide.

The rhesus monkey was studied with several agents because of the similarity of its placental structure to the human organ. Both are hemochorial placentas in which the maternal spiral arteries penetrate the base plate and send spurts of blood into the spaces between the chorionic villi (*29*). Unlike the human placenta, however, the rhesus placenta is commonly bidiscoid with the two discs connected by an interplacental artery carrying fetal blood.

The placental discs and major blood vessels of the rhesus monkey were resolved on camera images better with ^{99m}Tc-labeled red blood cells than with labeled proteins. This superior resolution may be due in part to less diffusion of the ^{99m}Tc indicator beyond the vascular compartment at 1 hr. However, the difference in vascular organ delineation may be attributable also to differences in organ distribution between the labeled red cells and plasma proteins. Gibson, et al (*30*) have shown that the hematocrit in muscle is only about half that of most visceral organs in the dog. Because the concentration of labeled red cells is considerably lower than labeled plasma proteins in muscle, vascular organs may be less obscured by the radioactive content of the surrounding musculature than in the case of a plasma label. The placenta may be regarded as a vascular organ since about 18% of its weight is blood (*31*).

The rhesus placenta was visualized somewhat better on camera images with ^{99m}Tc-albumin than with ^{113m}In. This is explained by the higher gamma energy and different collimator used for ^{113m}In. These images suggest, nevertheless, that the placental accumulation of ^{113m}In-transferrin may not be as high in primates as in rodents. The absence of urinary activity in the bladder is a distinct advantage of ^{113m}In over the ^{99m}Tc complexes.

The ^{99m}Tc-sulfur colloid, the only radioactive colloid tried in the rhesus monkey, produced relatively poor images of the placenta as might be expected from the rabbit distribution values. Provided that a short-lived radioactive colloid could be developed with extremely small particles, resembling a true radiocolloid in its distribution, the placental concentration should be improved. Such an agent could be useful for the determination of placental blood flow by external detection, by measurement of its rate of accumulation in the placenta following intravenous injection.

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